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| EXAMINER | |
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| **ART UNIT** | **PAPER NUMBER** |
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**Please find below and/or attached an Office communication concerning this application or proceeding.**

The time period for reply, if any, is set in the attached communication.

| Office Action Summary | Application No. | Applicant(s) | |
|---|---|---|---|
| | 10/622,293 | FREYMAN ET AL. | |
| | Examiner | Art Unit | |
| | QUANG NGUYEN, Ph.D. | 1633 | |

*-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --*

**Period for Reply**

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

**Status**

1)☒ Responsive to communication(s) filed on *14 May 2009*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

**Disposition of Claims**

4)☒ Claim(s) *1,5-27,30-35 and 42* is/are pending in the application.

4a) Of the above claim(s) *16-26,31-34 and 42* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1, 5-15, 27, 30 and 35* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

**Application Papers**

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

**Priority under 35 U.S.C. § 119**

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

**Attachment(s)**

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

## DETAILED ACTION

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 11/13/08 and 5/14/09 has been entered.

The amendment to the claims filed on 5/14/09 still does not comply with the requirements of 37 CFR 1.121(c) because the status of claim 42 is incorrect. It should be "Withdrawn" rather than "Previously presented" because claim 42 was already withdrawn in the Final Office action mailed on 8/19/08. However, for the purpose of a compact prosecution, the claim amendment filed on 5/14/09 was entered.

Amended claims 1, 5-27, 30-35 and 42 are pending in the present application.

Applicants elected previously Group I, drawn to a method for producing a decellularized extracellular matrix material containing a biological material or for producing a tissue regeneration scaffold for implantation into a patient wherein the step of conditioning a body tissue of a donor animal by genetic engineering and allowing the conditioned body tissue to produce the biological material are conducted prior to harvesting the conditioned body tissue from the donor animal. Applicants further elected the following species with traverse in the reply filed on 9/19/05, (a) bone marrow as a species of a body tissue; (b) VEGF as a species of a biological material; and (c) human as a species of a donor animal.

This application contains claims 16-26 and 31-34 drawn to an invention nonelected without traverse in the reply filed on 9/19/05.

Claim 42 was also withdrawn from further consideration because it is directed to a non-elected species.

Accordingly, amended claims 1, 5-15, 27, 30 and 35 are examined on the merits herein with the aforementioned elected species.

### *Sequence Non-Compliance*

This application contains sequence disclosures that are encompassed by the definitions for nucleotide and/or amino acid sequences set forth in 37 C.F.R. § 1.821(a)(1) and (a)(2). However, this application fails to comply with the requirements of 37 C.F.R. §§ 1.821-1.825 for the reason(s) set forth below.

This application contain the short peptide sequences RGD (see **at least** page 37, line7; page 40, line 19; page 41, line 8 and withdrawn claim 42) and D-Phe-Pro-Argchloromethyl ketone (page 41, line 8), however none of these peptide sequences **have been assigned with particular SEQ ID NOs. in either a paper sequence listing and/or computer readable form (CRF) of the sequence listing**.

### *Claim Rejections - 35 USC § 103*

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the

invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 1, 5, 8-15, 27 and 35 are rejected under 35 U.S.C. 103(a) as being unpatentable over Naughton (US 5,830,708; IDS) in view of Vituri et al. (Brazilian Journal of Medical and Biological Research 33:889-895, 2000; Cited previously), Mitchell et al (US 2002/0115208), Patel et al. (US 7,087,089) and Wolff et al. (WO 99/55379; IDS). ***This is a modified rejection.***

**With respect to the elected species**, Naughton teaches a method for producing a composition containing naturally secreted human extracellular matrix material, said method comprises the steps of: (a) culturing extracellular matrix secreting human stromal cells from tissues/organs obtained by appropriate biopsy or upon autopsy, including aspirated **bone marrow from normal human adult volunteers** (col. 5, lines 48-54; col. 15, lines 7-9), on a biocompatible three dimensional framework *in vitro*; (b) the stromal cells are killed after secretion of the extracellular matrix onto the framework and the cells and cellular contents are removed from the framework (col. 11, line 62 continues to line 63 of col. 12); (c) the extracellular matrix material deposited on the framework is collected and further processed to obtain a physiologically acceptable composition (col. 12, line 66 continues to line 20 of col. 14). Naughton further teaches that **it may be desirable to prepare an extracellular matrix containing a foreign gene product, growth factor, regulatory factor and in such a situation the cells are genetically engineered to express the gene product that is immobilized in the extracellular matrix laid down by the stromal cells** (col. 10, line 59 continues to line 22 of col. 11). **This is a conditioning step**. Naughton teaches that preferably, the

expression control elements used should allow for the regulated expression of the gene so that the product can be over-synthesized in culture (col. 11, lines 15-17). Furthermore, Naughton teaches that biologically active substances such as proteins and drugs can also be incorporated in the composition for release or controlled release of these active substances after injection of the composition that include tissue growth factors such as TGF-beta and the like which promote healing and tissue repair at the site of injection (col. 13, lines 12-22). Naughton teaches that **the extracellular matrix preparation is capable of promoting connective tissue deposition, angiogenesis, reepithilialization and fibroplasias, which is useful in the repair of skin and other tissue defects, and that the preparation is used to repair tissue defects by injection at the site of the defect** (col. 3, lines 43-48; col. 13, line 43 continues to line 20 of col. 14). It should be noted that the term "body tissue" is defined by the instant specification broadly encompasses any or a number of cells, tissues or organs (see page 7, lines 7-8).

Naughton does not specifically teach a method for producing a decellularized extracellular matrix containing a biological material, comprising the step of conditioning (**genetic engineering is the elected invention**) a body tissue (**bone marrow is the elected species**) of a donor animal (**human is the elected species**) in vivo to produce the biological material **prior to the step of harvesting the conditioned body tissue from the donor animal and decellularizing the conditioned body tissue**.

At the effective filing date of the present application, Vituri et al already demonstrated that **alterations in proteins of bone marrow extracellular matrix in**

**vivo could be achieved via protein malnutrition**, in which 2-month old male Swiss mice were submitted to protein malnutrition with a low-protein diet containing 4% casein (conditioning body tissue of a donor animal) as compared to 20% casein in the control diet, and when the treated mice had attained a 20% loss of their original body weight, extracellular matrix (ECM) proteins from bone marrow were extracted (a decellularization condition) and it was determined that bone marrow ECM from undernourished mice had greater amounts of extractable fibronectin and laminin (biological materials) compared to the control animals (see at least the abstract).

Additionally, Mitchell et al also disclosed methods for producing decellularized tissue engineered constructs and decellularized engineered native tissues for implanting into an individual in need thereof (see at least the abstract; Summary of the Invention), and taught that although in general the production of the tissue engineered construct involves culturing the developing tissue primarily *in vitro*, **tissue engineered constructs produced at least in part by culturing the tissue *in vivo* are also contemplated** (page 5, bottom of paragraph 67). Mitchell et al further taught that **there is a need to expose developing tissue engineered constructs to certain stimuli, so that the resulting construct develops properties and structure that more closely resemble those of the corresponding naturally occurring tissue** (paragraph 96).

Moreover, Patel et al also taught a process for preparing acellular extracellular matrix materials useful for supporting cell growth *in vivo* and *in vitro* (see at least Summary of the Invention). Patel et al further disclosed that **the acellular collagen-containing extracellular matrices can be derived from renal capsular tissues**

**harvested from either transgenic animals (pre-conditioned donor animal) or non-transgenic animals**, and that animals encompass mammals, preferably porcine, bovine or ovine (col. 3, lines 11-21).

Furthermore, Wolff et al also disclosed **a process for delivering a polynucleotide encoding a protein of interest (e.g., hormones, cytokines, growth factors and others) into parenchymal cells within tissues *in situ* and *in vivo*, including parenchymal cells of bone marrow within a mammal** (see at least Summary of the Invention; and page 8, second paragraph; page 7, first paragraph).

Accordingly, it would have been obvious for an ordinary skilled artisan in the art to modify the teachings of Naughton by also preparing a decellularized bone marrow extracellular matrix material harvested from the bone marrow of a donor animal, including a human donor, whose parenchymal cells of the bone marrow have been transfected with a polynucleotide encoding a protein of interest with or without a scaffold to heal and/or repair tissues in a patient in need thereof in light of the teachings of Vituri et al; Mitchell et al., Patel et al. and Wolff et al. as discussed above.

An ordinary skilled artisan would have been motivated to carry out the above modifications because acellular extracellular matrix materials useful for supporting cell growth *in vivo* and *in vitro* has been taught by Patel et al can be harvested from a transgenic animal or a pre-conditioned donor. Additionally, decellularized bone marrow extracellular matrix was also prepared by Vituri et al. from mice pre-treated or pre-conditioned *in vivo* with different diets prior to harvesting bone marrow extracellular matrix. Moreover, Mitchell et al also taught the preparation of decellularized tissue

engineered constructs and/or decellularized engineered native tissues, wherein there is a need to expose developing tissue engineered constructs to certain stimuli, so that the resulting construct develops properties and structure that more closely resemble those of the corresponding naturally occurring tissue. Accordingly, unlike the decellularized extracellular matrix prepared *in vitro* or in cultured conditions, the in vivo conditioned extracellular matrix (e.g., bone marrow extracellular matrix) would have properties, constituents and structure closely resemble those of corresponding naturally occurring extracellular matrix together with the incorporation of a desired protein of interest. Furthermore, Wolff et al already disclosed successfully a process for delivering a polynucleotide encoding any protein of interest in parenchymal cells of bone marrow within a mammal.

An ordinary skilled artisan would have a reasonable expectation of success to carry out the above modification in light of the teachings of Naughton, Vituri et al., Mitchell et al., Patel et al., and Wolff et al., coupled with a high level of skills of an ordinary skilled artisan in the relevant art.

Therefore, the claimed invention as a whole was *prima facie* obvious in the absence of evidence to the contrary.

***Response to Arguments***

Applicants' arguments related to the above modified rejection in the Amendment filed on 11/13/08 (pages 7-17) have been fully considered but they are respectfully not found persuasive for the reasons discussed below.

1. Applicants argue that the examiner has failed to establish a prima facie case of obviousness because the cited references failed to teach or suggest conducting steps (a) and (b) of independent claims 1 and 35 prior to harvesting step (c). With respect to the Naughton reference, Applicants argue that the reference is directed to in vitro cell culture techniques and not in vivo techniques, nor does the reference teach or suggest conditioning cells in vivo, including genetically engineering cells in vivo. Thus, the Naughton reference fails to provide any teaching or suggestion for either of steps (a) and (b) as recited in independent claims 1 and 35. With respect to the Mitchell reference, Applicants also argue that the reference also does not teach step (a) of conditioning body tissue of a donor animal in vivo to produce the biological material in an amount different than the amount of the biological material that the body tissue would produce absent the conditioning nor does the reference concern with genetic engineering of cells to express a foreign protein and/or conducting steps (a) and (b) prior to harvesting step (c). With respect to the Patel reference, Applicants also argue that the reference does not teach or suggest step (a), and that the examiner's citation to use of transgenic animals as a pre-conditioned donor animal does not amount to a teaching or suggestion to provide for conditioning in vivo. Further, even if use of transgenic animals was for some reason considers to be in vivo genetic engineering, there is no teaching or suggestion in Patel to indicate that the conditioning resulted in production of a biological material in an amount different than the amount of the biological material that the body tissue would produce absent the conditioning. Nor does the Patel teach or suggest the production of VEGF (the elected species) as the

biological material or any other biological agent or the conditioned body tissue is harvested and decellularized. With respect to the Wolff reference, Applicants also argue that the reference does not teach or suggest conducting steps (a) and (b), and particularly does not teach a harvesting step (c).

First, please note that the above modified rejection is made under 35 U.S.C. 103(a), and therefore there is no requirement that any of the cited references has to teach every limitation of the claims.

Second, on the basis of Applicants' arguments that are summarized above, it appears that Applicants only considered the teachings of each of the cited references in total isolation one from the others. Particularly, Applicants do not take into consideration of **all of the teachings of the cited references together**.

Third, with respect to the issue that there is no specific suggestion or teaching in the references to combine prior art, please note that KSR forecloses the argument that a **specific** teaching, suggestion, or motivation is required to support a finding of obviousness. See the recent Board decision *Ex parte Smith*, --USPQ2d--, slip. op. at 20, (Bd. Pat. App. & Interf. June 25, 2007).

Fourth, with respect to the issue of conducting steps (a) and (b) prior to harvesting step (c), see at least the teachings of Vituri et al in the above modified rejection. Additionally, it should be noted Patel already taught that that acellular collagen-containing extracellular matrices can be derived from renal capsular tissues harvested from either transgenic animals (**genetically modified and pre-conditioned donor animal**) or non-transgenic animals; indicating **at least at the effective filing**

**date of the present application decellularized extracellular matrix can be obtained from tissues derived from in vivo genetically modified animal donors, and not necessarily limited only to in vitro tissue cultures**. In comparison with a corresponding non-transgenic animal, the transgenic animal certainly produces a body tissue containing a transgene that a body tissue of the non-transgenic animal would not produce.

Fifth, the examiner notes that all of the above rejected claims do not recite specifically **all of the elected species**. With respect to the specific elected species VEGF recited specifically in an embodiment of claim 13 and in claim 30, please refer to the teachings of Herlyn et al. in the modified rejection below.

2. Applicants argue that one of ordinary skill in the art would not be motivated to combine reference teachings to lead to the presently claimed invention since each cited reference employs different body tissues and/or different techniques to achieve the desired objectives. Additionally, this is because Naughton's emphasis is on in vitro culturing of cells and there is nothing in Naughton that amounts to a suggestion to condition cells to express a foreign gene in vivo. Additionally, the Mitchell reference fails to provide the missing motivation to provide for in vivo conditioning, particularly genetic engineering which is the elected species, of cells because Mitchell's tissue engineered constructs produced at least in part by culturing cells in vivo does not concern genetic engineering of cells but rather pertains to growth in vivo on an artificial substrate. The examiner has not cited any information in Michell to provide for

motivation to genetically engineering cells in vivo. Both Mitchell and Naughton teach the criticality of growing cells in vitro. The Patel reference also does not provide the missing suggestion or motivation because in discussing transgenic animals Patel makes reference to an example of animals such as pigs raised for meat production and provides no motivation to modify the teachings of any of the previous references to provide for the production of VEGF (the elected species) or any other therapeutic agent in a donor human which is the elected species; and application of a technique to transgenic pigs modified for meat production does not amount to a suggestion or motivation to provide for genetic engineering of human cells to express a biological agent such as VEGF in vivo. The Wolff reference does not teach or suggest a method for production of a secreted extracellular matrix nor does the reference provide any suggestion or motivation to modify the teachings of Naughton or Michell. The examiner also has not provided any reasonable expectation of success for a modification of the method of Naughton or Mitchell in combination with Wolff and Wolff also does not provide any data setting forth delivery of a polynucleotide into bone marrow.

First, based on Applicant's above arguments once again it appears that Applicants try to seek an explicit suggestion or motivation in each of the cited references in total isolation and without taking into consideration of all of the teachings in the cited references. As already noted above, KSR forecloses the argument that a **specific** teaching, suggestion, or motivation is required to support a finding of obviousness. See the recent Board decision *Ex parte Smith*, --USPQ2d--, slip. op. at 20, (Bd. Pat. App. & Interf. June 25, 2007).

Second, please also refer to the Examiner' responses in section 1 above as well as the modified rejection as set forth above.

Third, an important concept that is taught by the Mitchell reference and is ignored by Applicants is the desire or a need to expose developing tissue engineered constructs to certain stimuli, **so that the resulting construct develops properties and structure that more closely resemble those of the corresponding naturally occurring tissue**. It is also noted that stimuli that are taught by Mitchell et all are not necessarily limited only mechanical or electrical stimuli, but they also include **chemical stimuli and others to produce a tissue engineered construct having desirable mechanical, physical or biochemical properties** (see at least paragraphs 67 and 76-77). Accordingly, unlike the decellularized extracellular matrix prepared *in vitro* or in cultured conditions taught by Naughton, **the *in vivo* conditioned extracellular matrix (e.g., bone marrow extracellular matrix) has properties, constituents and structure closely resemble those of corresponding naturally occurring extracellular matrix together with the incorporation of a desired protein of interes**t. Furthermore, Patel already taught that that acellular collagen-containing extracellular matrices can be derived from renal capsular tissues harvested from either transgenic animals (**genetically modified and pre-conditioned donor animal**) or non-transgenic animals; indicating **at least at the effective filing date of the present application decellularized extracellular matrix can be obtained from tissues derived from in vivo genetically modified animal donors, and not necessarily limited only to in vitro tissue cultures.**

Fourth, with respect to the issue of unreasonable expectation of success for the combined teachings of Naughton, Vituri et al., Mitchell et al., Patel et al., and Wolff et al. as set forth in the above rejection, the examiner is not clear exactly what is not reasonably expected, particularly in light of the teachings of Wolff for delivering a polynucleotide encoding any protein of interest in parenchymal cells of bone marrow within a mammal; decellularization processes for a harvested tissue from various sources as taught at least by Naughton, Mitchell, Patel; and the alteration of bone marrow extracellular matrix in animals that are conditioned in vivo via diets as taught by Vituri. Additionally, with respect to Applicant's argument that Wolff did not provide any data for delivery of a polynucleotide into bone marrow, the examiner notes that the instant specification also does not provide any data for delivery of a polynucleotide into bone marrow for any donor animal.

3. Applicants further argue that Wolff explicitly states that parenchymal cells are different from cells of the connective tissue and exclude fibrolasts (page 7, lines 16-20) and therefore teaches away from the stromal cells of Naughton. Based on the teachings of Wolff, a person of ordinary skill in the art would reasonably expect stromal cells and parenchymal cells to be structurally and functionally different and would each require a different approach for conditioning and culturing. Therefore, an ordinary skill in the art would have no motivation to combine the teachings of Wolff and Naughton.

There is no "teaching away" whatsoever by the Wolff reference with respect to the primary Naughton reference. Naughton stated clearly "**[s]tromal cells of**

**hematopoietic tissue including, but not limited to, fibroblast endothelial cells, macrophages/monocytes, adipocytes and reticular cells, can be used to form the three-dimensional subconfluent stroma for the production of a bone marrow specific extracellular matrix in vitro, see infra**" (col. 9, lines12-17). Additionally, Naughton **taught clearly culturing extracellular matrix secreting human stromal cells from tissues/organs obtained by appropriate biopsy or upon autopsy, including aspirated bone marrow from normal human adult volunteers** (col. 5, lines 48-54; col. 15, lines 7-9). Wolff stated "Parenchymal cells are the distinguishing cells of a gland or organ contained in and supported by the connective tissue framework. The parachymal cells typically perform a function that is unique to the particular organ. The term "parenchymal" **often excludes** cells that are common to many organs and tissues such as fibroblasts and endothelial cells within the blood vessels" (page 7, lines 17-21). **This paragraph simply distinguishes parenchymal cells and cells that are common to many organs and tissues**. Furthermore, Wolff stated "In spleen, thymus, lymph nodes and **bone marrow, the parenchymal cells include recitular cells and blood cells (or precursors to blood cells) such as lymphocytes, monocytes, plasma cells and macrophages**" (page 8, lines 4-6). Therefore, parenchymal cells in bone marrow taught by Wolff encompass stromal cells taught by Naughton.

4. Once again, Applicants argue that similar to the Lubowe patent in *In re Herschler*, the solution taught by Naughton is complete, and therefore it provides no

reason to look to the art for alternative steps to condition the cells and in particular no motivation to look to the transgeneic animal of Patel et al, the physical conditioning of Mitchell et al., and the polynucleotide delivery system of Wolf et al.

Once again, please note that KSR forecloses the argument that a **specific** teaching, suggestion, or motivation is required to support a finding of obviousness. See the recent Board decision *Ex parte Smith*, --USPQ2d--, slip. op. at 20, (Bd. Pat. App. & Interf. June 25, 2007). As already stated in the above modified rejection, an ordinary skilled artisan would have been motivated to modify the teachings of Naughton by also preparing a decellularized bone marrow extracellular matrix material harvested from the bone marrow of a donor animal, including a human donor, whose parenchymal cells of the bone marrow have been transfected with a polynucleotide encoding a protein of interest with or without a scaffold to heal and/or repair tissues in a patient in need because acellular extracellular matrix materials useful for supporting cell growth *in vivo* and *in vitro* has been taught by Patel et al can be harvested from a transgenic animal or a genetically modified pre-conditioned donor. Additionally, decellularized bone marrow extracellular matrix was also prepared by Vituri et al. from mice pre-treated or pre-conditioned *in vivo* with different diets prior to harvesting bone marrow extracellular matrix. Moreover, Mitchell et al also taught the preparation of decellularized tissue engineered constructs and/or decellularized engineered native tissues, wherein there is a need to expose developing tissue engineered constructs to certain stimuli, so that the resulting construct develops properties and structure that more closely resemble those of the corresponding naturally occurring tissue. Accordingly, unlike the decellularized

extracellular matrix prepared *in vitro* or in cultured conditions, the in vivo conditioned extracellular matrix (e.g., bone marrow extracellular matrix) would have properties, constituents and structure closely resemble those of corresponding naturally occurring extracellular matrix together with the incorporation of a desired protein of interest. Furthermore, Wolff et al already disclosed successfully a process for delivering a polynucleotide encoding any protein of interest in parenchymal cells of bone marrow within a mammal.

5. Finally, Applicants argue that the Examiner used hindsight reconstruction to pick and choose among isolated disclosures in the prior art to arrive at the presently claimed invention, and that this is improper when one of ordinary skill in the art would have no reason to combine the teachings of the references.

It must be recognized that any judgment on obviousness is in a sense necessarily a reconstruction based upon hindsight reasoning. But so long as it takes into account only knowledge which was within the level of ordinary skill at the time the claimed invention was made, and does not include knowledge gleaned only from the applicant's disclosure, such a reconstruction is proper. See *In re McLaughlin*, 443 F.2d 1392, 170 USPQ 209 (CCPA 1971). Please also refer to the modified rejection set forth above.

Accordingly, claims 1, 5, 8-15, 27 and 35 are rejected under 35 U.S.C. 103(a) as being unpatentable over Naughton (US 5,830,708; IDS) in view of Vituri et al. (Brazilian Journal of Medical and Biological Research 33:889-895, 2000; Cited previously),

Mitchell et al (US 2002/0115208), Patel et al. (US 7,087,089) and Wolff et al. (WO 99/55379; IDS) for the reasons set forth above.

Claims 13 **(VEGF embodiment)** and 30 are rejected under 35 U.S.C. 103(a) as being unpatentable over Naughton (US 5,830,708; IDS) in view of Vituri et al. (Brazilian Journal of Medical and Biological Research 33:889-895, 2000; Cited previously), Mitchell et al (US 2002/0115208), Patel et al. (US 7,087,089) and Wolff et al. (WO 99/55379; IDS) as applied to claims 1, 5, 8-15 and 27 above, and further in view of Herlyn et al. (WO 98/39035; Cited previously). ***This is a modified rejection.***

The combined teachings of Naughton, Vituri et al., Mitchell et al., Patel et al. and Wolff et al. were presented above. However, none of the references teaches specifically that bone marrow is transfected with a nucleic acid encoding VEGF.

However, at the effective filing date of the present application Herlyn et al already teach growth factors, particularly VEGF is useful in wound repair in mammalian tissue by enhancing fibroblast growth and formation into a matrix, enhancing keratinocyte growth and angiogenesis and *ex vivo* method for infecting tissue to be transplanted with a recombinant virus expressing VEGF prior to transplantation (at least page 6, lines 14-23).

Accordingly, it would have been obvious for an ordinary skilled artisan in the art to further modify the combined method of Naughton, Vituri et al., Mitchell et al., Patel et al. and Wolff et al. by also selecting VEGF as an foreign gene product to be

incorporated into the decellularized extracellular matrix in light of the teachings of Herlyn et al.

An ordinary skilled artisan would have been motivated to carry out the above modification because Herlyn et al already teach growth factors, particularly VEGF is useful in wound repair in mammalian tissue by enhancing fibroblast growth and formation into a matrix, enhancing keratinocyte growth and angiogenesis, and that this would enhance the clinical value for the composition containing the decellularized extracellular matrix material resulting from the combined teachings of Naughton, Vituri et al., Mitchell et al., Patel et al. and Wolff et al.

An ordinary skilled artisan would have a reasonable expectation of success to carry out the above modification in light of the teachings of Naughton, Vituri et al., Mitchell et al., Patel et al. Wolff et al., and Herlyn et al., coupled with a high level of skills of an ordinary skilled artisan in the relevant art.

Therefore, the claimed invention as a whole was *prima facie* obvious in the absence of evidence to the contrary.

Claims 6-7 are rejected under 35 U.S.C. 103(a) as being unpatentable over Naughton (US 5,830,708; IDS) in view of Vituri et al. (Brazilian Journal of Medical and Biological Research 33:889-895, 2000; Cited previously), Mitchell et al (US 2002/0115208), Patel et al. (US 7,087,089) and Wolff et al. (WO 99/55379; IDS) as applied to claims 1, 5, 8-15 and 27 above, and further in view of Schwarz et al. (US 6,656,916). ***This is a modified rejection.***

The combined teachings of Naughton, Vituri et al., Mitchell et al., Patel et al. and Wolff et al. were presented above. However, none of the references teaches specifically that a further step of delivering a therapeutic agent to the body tissue before or after the conditioning step.

However, at the effective filing date of the present application, Schwartz et al already taught **a method of increasing the cellular expression of a gene in a biological tissue in an animal, including a bone marrow in a human**, said method comprises administering to said animal a pharmacologically effective dose of a glucocorticoid in an amount sufficient to increase the cellular expression of said gene (see at least col. 2, lines 35-51; col. 5, lines 54-59). Schwartz et al taught specifically that any glucocorticoid such as hydrocortisone, prednisone, prednisolone, triamcinolone, betamethasone, budesonide, flunisolide and dexamethasone can be used (col. 5, lines 31-37). The glucocorticoid may be administered concurrently with the delivery of the gene, **prior to the delivery of the gene or after delivery of the gene** (col. 5, lines 48-51).

Accordingly, it would have been obvious for an ordinary skilled artisan in the art to further modify the combined method of Naughton, Vituri et al., Mitchell et al., Patel et al. and Wolff et al. by also administering to the donor animal a therapeutic agent such as a glucocoritoid to a body tissue prior to or after the gene delivery in light of the teachings of Schwarz et al.

An ordinary skilled artisan would have been motivated to carry out the above modification because the administration of a therapeutic agent such as a glucocorticoid

prior to or after the delivery of a gene would enhance the cellular expression of a delivered gene in a biological tissue, including a bone marrow in a human, as taught by Schwartz et al.

An ordinary skilled artisan would have a reasonable expectation of success to carry out the above modification in light of the teachings of Naughton, Vituri et al., Mitchell et al., Patel et al. Wolff et al., and Schwarz et al., coupled with a high level of skills of an ordinary skilled artisan in the relevant art.

Therefore, the claimed invention as a whole was *prima facie* obvious in the absence of evidence to the contrary.

***Response to Arguments***

Applicants' arguments related to the above modified rejection further in view of either Herlyn et al. or Schwarz et al. in the Amendment filed on 11/13/08 (pages 18-20) have been fully considered but they are respectfully not found persuasive for the reasons discussed below.

Applicants argue basically that neither Herlyn et al nor Schwarz et al cure the deficiencies of Naughton, Mitchell, Patel and Wolff because none of these references teaches or suggests performing a conditioning step (genetic engineering) of donor human in vivo prior to harvesting the conditioned body tissue from the human or any method for producing decellularized extracellular matrix material. Additionally, the examiner appears to be using hindsight construction to pick and choose from among the disclosures of the reference to arrive at the presently claimed invention.

With respect to the deficiencies of Naughton, Mitchell, Patel and Wolff as well as hindsight construction, please refer at least to the Examiner's responses to Applicant's arguments for the rejection of claims 1, 5, 8-15 and 27 above. Additionally, please refer to the motivations already set forth in the above modified rejections why an ordinary skilled artisan would be motivated to further modify the combined teachings of Naughton, Vituri et al., Mitchell et al, Patel et al and Wolff et al in light of the teachings of either Herlyn or Schwarz. Furthermore, please also note that the above rejections are made under 35 U.S.C. 103(a), and therefore there is no requirement that any of the cited references has to teach every limitation of the claims, including the teaching of a method for producing decellularized extracellular matrix material in either the supporting Herlyn or Schwarz reference.

## *Conclusion*

***No claim is allowed.***

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Quang Nguyen, Ph.D., whose telephone number is (571) 272-0776.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's SPE, Joseph T. Woitach, Ph.D., may be reached at (571) 272-0739.

**To aid in correlating any papers for this application, all further correspondence regarding this application should be directed to Group Art Unit 1633; Central Fax No. (571) 273-8300.**

**Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to (571) 272-0547.**

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/QUANG NGUYEN/

Primary Examiner, Art Unit 1633